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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,338	12/09/2004	Sven Ole Warnaar	2923-672	2944

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

NOTIFICATION DATE	DELIVERY MODE
08/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,338	WARNAAR ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,8-10,12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8-10,12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/9/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions including Applicants Declaration under 37 CFR 1.132 (Declaration) filed on February 26, 2008 have been entered.

Claims 1, 2, 4, 8-10, 12, and 14-18 are pending and under examination.

35 USC § 103(a) rejections maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-2, 4, 8-10, 12, and 14-18 under 35 U.S.C. 103(a) as being unpatentable over Bleumer et al., in view of Pavone is maintained.

Applicants argue that Applicants Declaration under 37 CFR 1.132 demonstrates that co-administration of an antitumor antibody (e.g. G250) and interferon (e.g. interferon-a) leads to an increased efficacy in the treatment of renal cell carcinoma as compared to administration of either G250 or interferon-a alone along with a reduction in side effects. Applicants argue that the increased efficacy is due to a synergistic effect

from the co-administration of the anti-tumor antibody and an interferon. Applicants further argue that this synergistic effect could not have been predicted from the disclosure in Bluemer which discloses only a monotherapy for treating RCC using the G250 antibody.

Applicants arguments have been considered but are not persuasive. Wiesenthal, Human Tumor Assay Journal, on-line (http://weisenthal.org/synergy1.htm, August 5, 2008) discusses the question of synergy between drug combinations and diseases. In particular, Weisenthal states that Combination chemotherapy frequently, but not always, has produced greater degrees of clinical benefit than single agent therapy." Wiesenthal further states that most "classic" drug combinations are only additive or are at most, minimally synergistic. Berenbaum ("Synergy, additivism and antagonism in immunosuppression," Clin exp Immunol, 1997, 28:1-18) disclose that to demonstrate the synergistic effect of two treatment agents, one must first prepare a dose-response curve for each agent alone (see Fig. 1 of Berenbaum). One must also prepare a number of combination treatments containing varying amounts of each agent. The results of all the treatments, each agent alone and the various combinations must be compared and analyzed quantitatively and statistically. The discussion on p. 2 of Berenbaum describes how the value obtained by measuring a response achieved by administering two pharmaceutical treatment agents is often mistaken for synergy when in reality it is the same as the effect obtained by using either agent alone. That is, the effect produced by administering agent A in a particular amount (e.g., x mg) and agent B in a particular amount (e.g., y mg) is the same as the one obtained by administering that total amount of agent A (x + y mg). Berenbaum also provides an algebraic method and a geometric method for determining the nature of the interaction of two agents (see pp. 3-5). To produce a graph such as Fig. 2 (p. 5), a particular response (effect) must be achieved by administering each agent alone. Different doses of agent A and different doses of agent B create the axes. A line is drawn between the two intercepts (the additivism line). A number of combinations of agent A and agent B, containing varying amounts of A and varying amounts of B, are tested, and the response is measured. The combinations producing the response achieved in the amount equal to

that of the intercept points are determined and plotted as data points on the graph. If these data points fall below the additive line, the effect of the combination is considered to be synergistic.

It is not clear from the clinical studies in Applicants Declaration that the administration of interferon- α and G250 had a synergistic effect compared to the administration of interferon- α alone and the administration of G250 alone. It appears that the studies primarily are evaluating combination therapies with G250 with IL-2 or G250 with interferon- α. In the clinical study from the Kidney Cancer Symposium in Chicago monotherapy with G250 was evaluated with combination therapies involving G250 and IL-2 or G250 and interferon- α. The combination therapy with G250 and interferon- α appeared to have a higher median overall survival rate and 2 year survival rate than the monotherapy fo G250 but whether the combination therapy had a synergistic effect over G250 and interferon- α alone could not be determined since montherapy with interferon- α alone was not performed. Applicants have not established that the combination therapy of interferon- α and G250 had a synergistic effect over the administration of G250 and interferon- α alone.

In addition, the results in the Declaration are not commensurate in scope with the claims. The results in the Declaration involve interferon- α and G250 while the claims except for claims are drawn to interferon and an antibody directed against the MN antigen.

Applicants also argue that if the pretreatment with IL-2 in Bleumer had been efficacious, then the G250 antibody would not have been administered. In addition, applicants contend that if Bleumer had expected the IL-2 to be efficacious, it would not have been considered a "pretreatment" prior to the administration of the G250 antibody. Applicants argue that since the purpose of Bleumer's study was to test the treatment of RCC with G250, IL-2 would not have been administered first if it was expected to be efficacious. Applicants argue that Pavone does not cure the deficiencies in Bleumer because Pavone does not disclose a synergistic effect either. Pavone teaches that IL-2 and IL-a have produced good results but does not suggest the combination of G250 and

IL-2 or IL-a. Applicants respectfully submit that one skilled in the art would not combine the disclosures of Bleumer and Pavone to arrive at the combined, simultaneous treatment required by the present claims because a skilled artisan is aware of the intractability of RCC to therapy and a skilled artisan would not have expected interferon α to be efficacious in treating RCC.

Applicants arguments have been considered but are not persuasive. Since Bleumer teaches the administration of both interferon α and G250 for the treatment of renal carcinoma, the teaches the use of both interferon α and G250 comprises a combination of ingredients known in the art to be useful for the same purpose, the claims are subject to an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine interferon α and G250, known to be useful in the treatment of renal cancer because the prior art teaches that both are useful for the treatment of renal cancer.

Summary

Claims 1, 2, 4, 8-10, 12, and 14-18 stand rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the

examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson
Patent Examiner
571-272-6539

/MISOOK YU/
Primary Examiner, Art Unit 1642